REMARKS

This Amendment amends claim 23 to expressly define oromucosal administration as absorption via oral mucosa. Page 3, lines 3-4 support this definition of oromucosal administration. One of ordinary skill in the art would understand "administration via oral mucosa" implicitly requires *absorption* via oral mucosa because no therapeutic benefit will result if an active ingredient is not absorbed by the body. Claims 23-32 are pending.

Examiner Gembeh is thanked for indicating the allowability of claim 30, if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. This Amendment places the entire application in condition for allowance for the reasons discussed below.

Examiner Gembeh is also thanked for the courtesies extended to the undersigned during an interview held August 8, 2008. The Examiner Interview Summary Record accurately reflects the substance of the interview.

The 35 U.S.C. § 103(a) rejection of claims 23-29, 31 and 32 over U.S. Patent No. 5,498,623 to Karjalainen et al. in view of U.S. Patent No. 5,658,938 to Geerts et al., U.S. Patent No. 6,326,401 to Chauveau et al., Huupponen et al., 58

Clin.Pharmacol.Ther. 506-11 (1995) and U.S. published application US 2004/0236108 to Smith et al., is traversed. The claimed method of administration requires a specified formulation be administered to a patient by oromucosal administration, defined as absorption via oral mucosa.

Oromucosal administration results in significantly greater bioavailability of the active ingredient in the claimed method in comparison to oral administration. See Example 7, in which plasma concentrations of fipamezole in healthy male volunteers were studied after oral administration as a solution vs. oromucosal administration as a tablet and as a spray. Table 1 on page 8 of the specification is reproduced below:

Table 1. Mean (SD) pharmacokinetic parameters of fipamezole at the dose level of 30 mg. t_{max} values are given as median and range.

30-mg dosing	C_{max} (ng/ml)	t_{max} (h)a	$t_{1/2el}$ (h)	$AUC_{0\text{-}inf}$ (ng*h/ml)
Oral	1.59 (0.38)	1.0 (0.75-2.0)	3.10 (2.23)	7.65 (2.99)
Oromucosal, tablet	31.74 (13.50)	0.85 (0.43)	3.10 (1.00)	115.6 (41.10)
Oromucosal, spray	49.2 (11.0)	0.7 (0.5-1.0)	2.10 (0.20)	157.1 (24.7)

C_{max}, maximal drug concentration in serum; t_{max}, time of maximal drug concentration in serum; $t_{1/2el}$, apparent elimination phase half-life; AUC_{0-inf}, area under the drug concentration in serum *vs.* time curve from time 0 to infinity.

The significantly greater bioavailability of fipamezole when administered oromucosally is illustrated in Fig. 1, which compares mean plasma concentration vs. time for oral administration vs oromucosal spray and oromucosal tablet administration. It should be noted the fipamezole concentration scale is logarithmic.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method because one of ordinary skill in the art would not combine their disclosures as suggested by the Patent Office, or have a reasonable expectation that the combination would be successful. Karjalainen et al. fails to disclose or suggest oromucosal administration of its composition. Instead, Karjalainen et al. discloses its compounds may be administered orally, parenterally or intravenously (Col. 4, lines 60-64). One of ordinary skill in the art would understand "oral administration" is not administration via oral mucosa (such as the alveolar mucosa, gingival mucosa and pharyngeal mucosa). Instead, formulations which are orally administered are designed to be swallowed and distintegrate/dissolve in the gastric tract to permit absorption, typically in the duodenum.

Geerts et al. also fails to disclose or suggest oromucosal administration of a substituted imidazole conforming to formula (I). Instead, Geerts et al. teaches oral, parenteral or rectal administration of its substituted imidazoles (Col. 10, lines 46-62). One of ordinary skill in the art has no apparent reason or motivation from Karjalainen et al. or Geerts et al. to administer the substituted imidazole of formula (I) via the oral mucosa.

The remaining references also fail to provide the motivation absent from Karjalainen et al. and Geerts et al. Thus, Chauveau et al. provides a narrow disclosure of oromucosal formulations which contain an active ingredient in combination with less than 5 % of capryl caproyl macrogel glycerides. The entire thrust of Chauveau et al. is directed to the utility of capryl caproyl macrogel glycerides in such formulations. See Col. 5, lines 16-59. One of ordinary skill in the art is thus given no apparent reason to modify Karjarlainen et al. to arrive at the claimed invention.

Huupponen et al. differs from the claimed invention because atipamezole does not contain a halogen or hydroxyl at R_1. Neither halogen or hydroxyl are bioisoteric with the hydrogen in atipamezole. Accordingly, one of ordinary skill in the art would not be motivated to substitute Karjalainen et al.'s substituted

imidazole for Hupponen et al.'s atipamezole. Moreover, one of ordinary skill in the art would not have a reasonable expectation that such a substitution would be successful, due to the known problem of cardiac safety associated with fipamezole, discussed below.

One of ordinary skill in the art would not be led to the claimed method by Smith et al., which is directed to carbocyclic hydrazino inhibitors whose structure significantly differs from the substituted imidazole of the claimed method due to their lack of an imidazole ring.

Those of ordinary skill in the art would not have a reasonable expectation of success in performing the claimed method. Oral administration of a substituted imidazole derivative conforming to formula (I) has been associated with compromised cardiac safety at systemic concentrations of about 2000 ng/ml (Specification, page 1, line 31 to page 2, line 2 and Example 8). Oral administration requires the drug to pass through the liver - and be subject to metabolic action - before reaching the heart. A person of ordinary skill would assume oromucosal administration of fipamezole would compromise cardiac safety to a greater extent than oral administration due to its significantly greater bioavailability

when oromucosally administered - the drug would be absorbed through the oral mucosa into the bloodstream and then carried directly to the patient's heart without any reduction in dosage due to metabolic action. Accordingly, one of ordinary skill would not have a reasonable expectation that oromucosal administration of fipamezole would be successful.

Finally, the unexpected results achieved by oromucosal administration rebut any prima facie case of obviousness. As noted above, oral administration of a substituted imidazole derivative conforming to formula (I) has been associated with compromised cardiac safety at systemic concentrations of about 2000 ng/ml. The applicants discovered fipamezole's problems of compromised cardiac safety and rapid decomposition can unexpectedly be avoided by oromucosal administration even at systemic concentration levels of up to 3,300 ng/ml.

Example 8 evaluated cardiac safety of fipamezole when orally administered v. oromucosally administered to dogs. QT prolongation was observed when the systemic concentration of fipamezole administered orally reached about 2000 ng/ml. Conversely, no QT changes (Q-Tcv or QTc) were observed in dogs administered buccal

spray doses of fipamezole at the same dosage (10 mg/kg).[1] This is especially surprising because the increased bioavailability of fipamezole achieved by oromucosal administration resulted in plasma concentrations of about 3300 ng/ml at the 10 mg/kg dosage level.

Nothing in the cited references suggests oromucosal administration of fipamezole will avoid the problem of compromised cardiac safety. Accordingly, the results shown in Example 8 would be considered unexpected by one of ordinary skill in the art.

Reconsideration and withdrawal of the obviousness rejection of claims 23-29, 31 and 32 are earnestly requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 23-29, 31 and 32, and issuance of a Notice of Allowance directed to claims 23-32, are respectfully requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

It is not believed any fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is

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[1] QT prolongation is a heart condition associated with prolongation of cardiac ventricle repolarization (recovery) following depolarization (excitation). It is associated with fainting and sudden death due to ventricular arrhythmias.

authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

James C. Lydon
Reg. No. 30,082

Atty. Case No.: **TUR-168**
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447